Roundtable Discussion

A Conversation With Drs. Kaplan and Moser About Conflicting Data, Confusing Results, and Some Recent Treatment Recommendations for the Management of Hypertension

Wendy Post, MD, MS; Marvin Moser, MD; Norman Kaplan, MD

Following a hypertension symposium in Baltimore, MD, on June 1, 2005, Dr. Wendy Post from the Johns Hopkins University School of Medicine, Baltimore, MD, had the opportunity to interview two of the outstanding hypertension experts in the United States on several controversial issues in hypertension management. Dr. Norman Kaplan is Clinical Professor of Medicine at the Southwestern Health Science Center in Dallas, TX, and Dr. Marvin Moser is Clinical Professor of Medicine at the Yale University School of Medicine, New Haven, CT. Both have been leaders in the field of hypertension treatment and education for more than 40 years. Dr. Kaplan's book Clinical Hypertension *has been a standard textbook since 1973 and is now in its ninth edition. Dr. Marvin Moser was the Senior Medical Consultant to the National High Blood Pressure Education Program from 1974 to 2002 and was Chairman of the first Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure and a member of the six subsequent committees. His book* Clinical Management of Hypertension *is in its seventh edition. Drs. Moser and Kaplan were corecipients of the 2004 International Society of Hypertension Award for Outstanding Contributions to Hypertension Treatment and Education and have lectured extensively throughout the United States and overseas. (J Clin Hypertens. 2005;7:606–611)* ©2005 Le Jacq Ltd.

DR. POST: Let's start with a truly controversial topic. The Seventh Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) designated blood pressures (BPs) of 120/80–139/89 mm Hg as prehypertension. Dr. Kaplan, do you think this was a good idea or should we still use the high-normal designation for these patients? Do you think labeling is useful or anxiety-producing?

DR. KAPLAN: I think it's probably both, but overall I believe that the term has value, mainly as a motivator for both patients and physicians to at least be aware that there may be some cardiovascular risk at these levels of BP and therefore to encourage the use of lifestyle modifications. The JNC 7 report clearly stated that this designation was not to be taken as an indication for active drug therapy, but rather as an indicator that appropriate lifestyle modifications should be followed.

The term *prehypertension* may also cause anxiety, and I don't think we should simply be telling people that they've got prehypertension without a full explanation of what it means; however, in the future we may want to treat more of these patients with medication. There is one trial in progress, the Trial of Preventing Hypertension (TROPHY), which is examining the value of antihypertensive drug therapy in patients who are prehypertensive. The study is not designed as an outcome trial; that would take a much bigger study, but simply to determine whether therapy can slow the progression of prehypertension into overt hypertension.

When that trial is completed and published, within about a year, we may argue more about active drug therapy in many of these patients. But at the moment, I do not think that drug therapy is indicated unless the patient has a number of other major risk factors in association with this level of BP.

DR. MOSER: You can't argue with the fact that people with pressures in the range of 130–140/80–85 mm Hg may be at greater risk than those below 120/80 mm Hg, but the risk is quite minimal unless there are other cardiovascular risk factors present. I still believe that we should have kept the high-normal designation for at least one reason: when you say prehypertension, it does result in some people being concerned that they have a disease. The JNC 7 committee didn't intend for this to happen. But, on the other hand, I also know that the designation may alert physicians to do something about these pressures in terms of lifestyle changes and I couldn't agree more with Dr. Kaplan. People who are obese, who have evidence of the metabolic syndrome with low HDL or elevated triglyceride levels, or have borderline fasting blood glucose levels with these BP values should be strongly encouraged to follow recommendations for weight loss, sodium restriction, etc. But as the European Society of Hypertension report said very clearly, prehypertension might be hypertension in someone with these risk factors but it is quite normal in someone who is thin and has no other cardiovascular risk factors.

So, I think the term is a double-edged sword. There is some advantage to alerting physicians to change their approaches and alerting patients to change their habits, but there is some danger in labeling and producing unnecessary anxiety. At the moment we have no evidence, except perhaps in patients with the metabolic syndrome, that these people should receive any specific medical therapy other than lifestyle changes.

DR. POST: But, perhaps, with the epidemic of obesity and the metabolic syndrome, it can't hurt patients to get an even stronger message about the importance of lifestyle modifications. Primary care physicians might wish to incorporate knowledge of other risk factors in determining how strongly to emphasize the importance of prehypertension as a risk factor.

DR. MOSER: But be careful about the way you approach the problem and what you say to patients.

DR. POST: So that you don't produce anxiety.

DR. MOSER: When you tell someone that they have a high-normal BP and that they should reduce their weight, restrict sodium, etc., it is quite different from telling them that they are prehypertensive. Some of these patients are going to walk out of your office and consider that they are ill. So I think you have to be careful.

DR. KAPLAN: Dr. Tom Pickering, in an editorial in a recent issue of *The Journal of Clinical Hypertension,* pointed out that there are about 60 million people in the United States with prehypertension, which is as many as we have identified with actual hypertension and BPs >140/90 mm Hg. I think Tom very wisely pointed out that we're not doing an adequate job in taking care of those who have BPs above 140/90 mm Hg. Therefore, to add an additional burden to physicians' responsibilities of trying to deal with another 60 million people may really not be utilizing our resources as well as we should.

DR. MOSER: Good point. I think Tom titled the editorial "Is Anyone Still Healthy?"

DR. KAPLAN: Yes.

DR. POST: Not an easy issue to settle. Our next question is: Is it BP lowering or specific medications that make the difference in determining clinical outcome? Do you want to start, Dr. Moser?

DR. MOSER: I think Norm and I will probably agree on this. I believe that most of the time it's the achieved BP level that determines outcome. Almost all of the clinical trials are very clear about this—the lower the BP, the better the outcome, regardless of how it's achieved. There are, however, some exceptions. Probably anyone with renal disease, diabetes, or even microalbuminuria without proteinuria or an elevated creatinine level would benefit if an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) were used as part of therapy, usually with a diuretic. The diuretic is necessary because BP is not going to be reduced to goal levels without it. The answer is that I believe that 80% or 90% of the time it's the BP level that makes the difference, but there are some cases where specific drugs are indicated.

DR. KAPLAN: In general, I agree that it is the degree of BP reduction that one achieves that is the critical issue. But as Marv and I both are aware, the Joint National and International Committees have pointed out that there are so-called specific compelling indications for recommending one or another type of drug for certain types of patients. One obvious example, as Marv pointed out, are people with proteinuria where ACEIs and ARBs have a particular advantage. But, in fact, the reduction in BP even with these agents is probably more important than the use of a specific drug. When we look at the overall picture, it doesn't really matter. It's getting the BP down in whatever manner is acceptable to the patient.

There are many patients, such as people with prostatic hypertrophy, where α blockers have a place, or patients with angina where β blockers are useful, etc. Specific medications may be indicated for individual patients.

DR. MOSER: Let me emphasize a point. We talk about using a specific drug for compelling indications, for example, diabetic nephropathy and ACEIs or ARBs, but all of the trials that have done this were not really ACEI or ARB studies, they were studies of ACEIs or ARBs plus other therapies, usually a diuretic. In most of these people, even with specific or compelling indications, two or more different drugs may have to be used.

DR. KAPLAN: Right. That is certainly something that has become more and more obvious, in part because we have lowered the level of BP that we believe is an appropriate goal of therapy. For diabetics and renal patients, 130/80 mm Hg is now considered the appropriate goal. It has been pointed out many times that to achieve even 140/90 mm Hg and certainly 130/80 mm Hg, it's going to take more than one drug. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) experience is typical. About two out of three of the patients who entered ALLHAT required two or more drugs to achieve BP control of 140/90 mm Hg. And the ALLHAT population did not include severe hypertensives; I think their average BPs were about 148/95 mm Hg. So, for many patients, we now have to turn from worrying about which is the best one drug to which is the best combination of drugs.

DR. POST: There seems to be an agreement on that subject. Now we have a number of new clinical trials that have been announced in recent years. How does a clinician decide which clinical trial results he or she should believe since conclusions often differ? For example, ALLHAT in the United States seemed to conflict with results of the Australian National Blood Pressure 2 (ANBP-2) study—and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) results, where final results are not yet available, appear to differ from those of the Swedish Trial in Old Patients with Hypertension-2 (STOP 2). Can you put this into perspective?

DR. KAPLAN: As you look at all the meta-analyses that have been published, there is still one overall conclusion, and that is: the lower the BP, the better. One could point out that the ALLHAT population, which included a large number of African Americans who respond somewhat differently to medications than nonblacks, is quite different than the Australian trial, which was an exclusively Caucasian population. There are differences, therefore, within different populations that have been looked at. But everything points to the fact that, as Marv stated, better protection against both coronary disease and stroke is achieved by the greatest reduction in BP, regardless of how that's achieved.

DR. MOSER: I would agree with that completely. It is difficult for the practicing physician to look at the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE), ASCOT, Australian, or ALLHAT results and reach any conclusion regarding specific therapies. These trials included different populations, different ages, different risk factors, and different combinations of drugs. The bottom line again is to get the BP as low as you can and, to do this, you will probably need a combination of medications. In my judgment, a diuretic should be part of therapy, but some people would disagree with that. So, the individual trial results may appear to be confusing, but when they are analyzed together the message is quite clear.

DR. KAPLAN: I believe that many of us, certainly among the experts in the field who spend a lot of our time and energy looking at these data, are still perplexed. The average practitioner who really doesn't have the time and patience to review all of the trial data certainly can be confused by the differences that have been reported. When it comes down to it, we have to recognize that no trial has been carried out exclusively with a single drug compared with another single drug. I think Dr. Moser pointed this out a few minutes ago; that in all of the trials, the majority of patients ended up on other drugs in addition to the study drug.

A good example would be the Losartan Intervention For Endpoint (LIFE) reduction in hypertension trial, which has been very heavily promoted to indicate that one of the agents tested, an ARB, was superior to a β blocker in reducing strokes. And I believe that. But one has to appreciate that 80% of the patients on either of those agents were also receiving a diuretic. So to say that the results were due to the single drug being better than another drug, I think, is a mistake.

DR. POST: Again, a basic agreement regarding this major question—Is it the BP or specific medication? Now, another point. An interesting result of the recent clinical trials has been the finding that suggests that patients on ACEIs or ARBS may be at a decreased risk, whereas those randomized to diuretics or β blocker-based therapies may be at increased risk for developing new-onset diabetes. There is a conflict that relates to how important new-onset diabetes is as a result of medical therapy. What are your thoughts about the prognosis of

new-onset diabetes? Is it similar to that of preexisting diabetes, does its occurrence affect outcome, and should there be concerns for new-onset diabetes as an important influence in terms of choice of initial antihypertensive therapy?

DR. MOSER: Data in placebo-controlled trials years ago indicated that diuretics increased new-onset diabetes by less than 1%. The newer trials report 30%, 43%, or 20% relative increases, but absolute increases of only about 1%–3.5% with β blocker/diuretic-based therapy compared with ACEI/ARB-based treatment. Now, that's an important number if you're in the 1%–3% group. The debate is not over the fact that perhaps the use of a diuretic or particularly a β blocker may increase new-onset diabetes more than other medications; the debate is over its significance.

Years ago, Gurwitz and, more recently, Gress reported that there were no differences in new-onset diabetes in people on any of the particular drugs, including ACEIs and diuretics, except that Gress reported an increase with β blockers. Both of these studies, however, were retrospective or not well controlled.

The Verdecchia study from Italy, which has recently been publicized, was not a very well controlled study as well, with a median 6-year follow-up. He reported that new-onset diabetics appeared to have the same prognosis as diabetics pretreatment. There are many problems with this study. There were few events. The baseline was at 3 years and, at the end of 10–16 years, outcome was determined. There are few data about treatment, BPs, etc., in between. That study indicated that if new-onset diabetes has the same prognosis, then you want to stay away from drugs that may increase its incidence. In fact, Norm, you know that some of our colleagues called for FDA warnings and some of them called for modifications of the JNC recommendations.

The Systolic Hypertension in the Elderly Program (SHEP) follow-up study has recently been published. At the end of the 5-year controlled trial, people were followed for mortality data without attention to BP levels or drugs used. In this study, patients in the chlorthalidone group who developed new-onset diabetes did not have the same prognosis as diabetics pretreatment. In fact, the prognosis in the treated group was better than the diabetics.

I believe that at the moment we do not have compelling or consistent trial evidence to make a judgment. I don't believe that we should tell practitioners that there is enough evidence to act on the question of medication choice and new-onset diabetes. We do, however, have a clue. In the Verdecchia series, people who developed new-onset diabetes had higher systolic and diastolic pressures, more left ventricular hypertrophy, and signs of the metabolic syndrome at baseline. So perhaps the message should be that if you've got a patient with these findings, an ACEI or an ARB should be started and then a diuretic added, rather than starting with a diuretic and adding an ACEI or an ARB if they don't respond. I don't know, Norm, how does that sound?

DR. KAPLAN: Let me just very quickly point out again that the study in Italy had a rather small number of events. But these patients were on combination therapy. They blamed it all on the diuretic when it could have been other parts of therapy. This is particularly true with the combination with β blockers. As you pointed out, the Gress study and others have shown that there is a worsening of glucose tolerance and a reduction in insulin sensitivity with β blockers in general.

I think that when Dr. Moser and I were just getting started, diuretics were used in very high doses; there was probably an effect on glucose metabolism with these doses. But through the years we've all learned that it doesn't take more than 12.5 mg in most people and certainly no more than 25 mg of hydrochlorothiazide to get the full benefit as far as the antihypertensive effect of a diuretic. Sometimes, of course, if people have renal insufficiency we may have to use stronger diuretics, but as far as the use of hydrochlorothiazide, I think 25 mg turns out to give as good an antihypertensive effect as we're going to get.

One of the other studies that has been used to cast aspersions against diuretics is ALLHAT. Chlorthalidone was given in doses up to 25 mg, which would be equivalent to about 40 mg of hydrochlorothiazide. Chlorthalidone is both stronger and longer acting than hydrochlorothiazide. There was an 11.6% incidence of new-onset diabetes among patients given chlorthalidone, compared with a 9.8% incidence in patients who were given a calcium channel blocker (CCB) and 8.1% with an ACEI.

Therefore, I think that higher doses of diuretics and β blockers may present a problem as far as provoking diabetes. And I think we shouldn't be using high doses of diuretics or β blockers, except when there are specific indications, because I think that the additional insult of new-onset diabetes can't be good for the patient.

DR. MOSER: Norm, other than in the patient with metabolic syndrome findings, let's say an

obese person with a low HDL and a high triglyceride level, would you change your recommendations about using a diuretic as first-step therapy in most people?

DR. KAPLAN: Well, I would certainly stay with low doses, but I would not withhold a diuretic from a patient who is obese and has dyslipidemia and other features of the metabolic syndrome. I would use any medications necessary to lower BP. As I think we've pointed out before, with whatever other drugs we choose, a diuretic is oftentimes needed to get adequate control of the BP.

DR. MOSER: And the obese patient is often volume overloaded and may need a diuretic.

DR. KAPLAN: Exactly.

DR. POST: So, new-onset diabetes may be a problem but, at present, outcome does not appear to be affected and drug choice may not have to be modified. The last question today involves the recommendations of JNC 7 to use combination therapy as initial treatment in patients with stage 2 hypertension; that is, BPs above 160/100 mm Hg, or even in some patients with stage 1 hypertension, 140/90 mm Hg–160/100 mm Hg, who have coexisting morbidities such as diabetes or renal disease. Dr. Moser, can you comment on these recommendations?

DR. MOSER: Well, I think they're quite valid. Most patients with 160 mm Hg or higher systolic pressures are not going to respond to one medication. The question is, if most of them require two medications, why not use two different drugs instead of a combination pill? That's an argument that has a lot of validity, because using a generic ACEI, for example, and a generic diuretic might produce exactly the same results in terms of BP lowering as a combination of an ACEI/diuretic or ARB/diuretic. There is, however, some evidence from the literature that using a combination is more effective. Titration to an effective dose is usually easier, patient visits are less frequent, costs may not be increased at all because there are fewer copayments, and the patients' perception of their illness might be changed. I believe that this is because a lot of patients are on NSAIDs, antidiabetic drugs, aspirin, and lipid-lowering medications and the addition of one pill instead of two, two instead of four, has been shown to have a beneficial psychologic impact on the patient.

The other recommendation about stage 1 hypertension with other comorbidities, especially diabetes or renal disease, is also valid. Most of these people do not respond to monotherapy. The ones who respond to monotherapy, and certainly Norm has had a lot of experience with this, are the people with stage 1 hypertension who do not have other comorbidities, who are not obese, and are not diabetic. These are the patients in whom monotherapy is probably successful in more than 60% of cases. There are, of course, some patients with stage 2 hypertension who may also respond, but the percentages are less. But in most patients, I believe that the JNC 7 recommendation is valid. This may be of concern to some of our academic colleagues.

DR. KAPLAN: Well, let me just say that I have seen an occasional patient with those levels of BP who did get a good response to one drug. The only other group in which I would be a little bit hesitant about starting two drugs would be in the elderly with systolic pressures above 160 mm Hg. Most of these patients will have pure isolated systolic hypertension. I would be cautious about lowering their BP by using fairly high doses of combinations. I have no problem with starting virtually everyone on lower doses of combination drugs. The higher the level of pressure, the more likely they're going to require more than one drug.

Perhaps another caution that might be interjected is that we want to be sure that the level of BP has been well documented. Unfortunately, a lot of people are given a diagnosis of hypertension and started on treatment on the basis of one or two casual BPs. One thing we have learned is that oftentimes it takes multiple BPs and out-of-the-office BPs to document the diagnosis of hypertension.

Now, of course the presence of other risk factors like diabetes would indicate the need for combination therapy even at much lower BPs than 160/100 mm Hg. Fortunately, I think the pharmaceutical industry has been appropriately responsive to the value of a low-dose thiazide diuretic. I think that virtually every class of drug, except for the CCBs, are being marketed with a low-dose thiazide plus a β blocker, ACEI, or ARB, so that the use of these combinations does seem to me to be a very rational approach for many of our patients.

DR. MOSER: What you said, Norm, is worthy of emphasis. Many elderly patients will have systolic pressures above 160 mm Hg, which would put them in stage 2 hypertension. I think you're right; you could start with monotherapy and go slow if any symptoms are noted.

DR. KAPLAN: I think this is particularly important in the elderly who are prone to have postural hypotension without therapy. We should be cautious about giving more therapy on the basis of office BPs, which may be transiently higher than pressures at home.

DR. MOSER: I can't resist two questions. First, which pressure do you use in the elderly to determine treatment? Upright or sitting?

DR. KAPLAN: Well, I think we ought to take an upright pressure but, in general, we still should judge therapy by the sitting BP.

DR. MOSER: Second, since all of the data on outcome and all the data on risk are based on casual pressures, why would we decide to use home BPs as a measure of how to treat someone?

DR. KAPLAN: You're right, when you look at the overall effect of BP in large populations, it's clearly based on office readings. All of the databases that we have used to assess risk of BP have essentially been based on one or two office BPs. But to avoid overtreatment, I still believe that home BPs can be very valuable, much more so than I think we've appreciated. But at present, we still don't have large outcome trials that have shown us that they are clearly superior. In fact, in a number of recent papers, it appears that out-of-the-office BPs really do not give a great deal more prognostic information than do office pressures. Individual patients, however, may have considerably lower BPs at home that at least would concern me about postural hypotension. Therefore, I would like to have patients take their own BPs. I think we're going to come around to that more and more. Home monitoring is becoming more popular and the machines are easier to use and more accurate, so I believe that in the future we're going to be depending more and more on home monitoring. But, again, we should not neglect the readings that have been taken in the office.

DR. MOSER: On a closing note, just to differ a little bit, I think that if I were being treated, I would prefer to have my casual pressure in the office lowered to normal unless I had been having symptoms at home. How does that sound? And, as an older person, I might want medication regulated by standing BPs.

DR. KAPLAN: I don't want to wait for symptoms to call attention to the possibility that there's a "white coat" effect when the pressures have only been measured only in the office. To identify this and hopefully prevent the possibility of postural falls and difficulties with too low pressures, we should monitor for diastolic BPs below 60–65 mm Hg. Particularly in the elderly who may have pure isolated systolic hypertension with a diastolic of 70 mm Hg, it's not at all unusual to see these go down to 60 mm Hg on therapy. I'm just a little bit concerned when that happens, and therefore I might back off a bit or at least go slower in reducing the BP in people when there is a significant fall in pressure or a significantly lower BP obtained out of the office.

DR. POST: Well, thank you, Drs. Moser and Kaplan, for the opportunity to hear your opinions about some ongoing controversies in the management of hypertension. I would like to summarize briefly. We have discussed prehypertension and the recognition of prehypertension as an indication for lifestyle modification with a word of caution to prevent anxiety by labeling. We also discussed conflicting clinical trial results as perhaps not being as confusing as they may first appear. The overall message is getting the BP down to goal and that most patients will need multiple medications to do this.

We talked about new-onset diabetes possibly associated with diuretics and β blockers compared with some other medications and how we might consider the use of an ACEI or an ARB in a patient at risk for developing diabetes in combination with low doses of diuretics.

We also discussed combination therapy as a rational approach to treating patients with stage 2 hypertension, but that we should be especially cautious in the elderly, in whom we need to lower BP more slowly, and that we should consider monitoring BP at home, especially in the elderly, with some caution when very low diastolic BPs are obtained.